IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Lennart CEDGARD

Application No.:	09/465,667	Art Unit:	1651
Filed:	December 17, 1999	Examiner:	Afremova, V.

Title: METHOD FOR THE PRODUCTION OF TABLETS BY PRESSING AND TABLETS PRODUCED BY THE METHOD

DECLARATION UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Henning G. Kristensen, hereby declare that:

1. I am a citizen of Denmark residing in Denmark.

2. My formal education includes attendance at the Royal Danish School of Pharmacy in Copenhagen, Denmark, where I received my Masters in Pharmacy in 1963. In 1968 I received my PhD from the Department of Pharmaceutics at the Royal Danish School of Pharmacy. I also received my Doctor of Pharmacy from the Royal Danish School of Pharmacy in 1981.

3. From 1968-1970, I was an Assistant Professor in the Department of Pharmaceutics at the Royal Danish School of Pharmacy. From 1970-1973, I was a Research Fellow and from 1973-1977 I was an Associate Professor in the same department. In 1978 I became a Full Professor of Pharmaceutics, and remain a Full Professor of Pharmaceutics at the Royal Danish School of Pharmacy today. Particular fields of research and teaching in which I specialize are the formulation, processing, and quality control of oral drug products, in particular solid dosage forms such as tablets and capsules. I possess the requisite knowledge related to the quality requirements of raw materials for the manufacture of drug products and the quality requirements or drug products.

4. Through a combination of education and experience I am a skilled worker in the field of pharmaceuticals and pharmaceutical formulation. I have reviewed and understand U. S. Patent Application No. 09/465,667 ("the '667 application"). I am also familiar with the Office Action dated January 13, 2004.

5. Based on my background and experience in the field of pharmaceuticals and pharmaceutical formulation, it is my opinion that at the time of the invention of the subject matter disclosed in the '667 application, a person having ordinary skill in the art of pharmaceutical formulation would not have combined the features of the cited patent references to arrive at the invention set forth in each of the claims of the '667 application, for reasons set forth more clearly below.

6. Attached and labelled as Kristensen Declaration Exhibit 1 is a true copy of the '667 application as filed with the United States Patent and Trademark Office.

7. Attached and labelled as Kristensen Declaration Exhibit 2 is a true copy of the claims presently on file in the '667 application

8. Attached and labelled as Kristensen Declaration Exhibit 3 is a true copy of the Office Action dated January 13, 2004, containing the above-mentioned rejection of the claims of Exhibit 2.

9. Attached and labelled as Kristensen Declaration Exhibit 4 is a true copy of U.S. Patent No. 4,396,631 Adachi et al.

10. Attached and labelled as Kristensen Declaration Exhibit 5 is a true copy of U.S. Patent No. 5,536,526 to Virtanen et al.

11. Attached and labelled as Kristensen Declaration Exhibit 6 is a true copy of U.S. Patent No. 5,531,989 to Paul.

12. Attached and labelled as Kristensen Declaration Exhibit 7 is a true copy of U.S. Patent No. 5,422,346 to Mitchell et al.

13. Attached and labelled as Kristensen Declaration Exhibit 8 is a true copy of U.S. Patent No. 4,021,545 to Nair et al.

14. Attached and labelled as Kristensen Declaration Exhibit 9 is a true copy of U.S. Patent No. 4,806,368 to Reddy.

15. Hereafter the patents mentioned in paragraphs 9 to 14 will be referred to by the first inventor name, or by their Exhibit number. The other exhibits will simply be referred to by their Exhibit number.

16. The Office Action of January 15, 2004, rejects all pending claims, Claims 11, 12, 14-27 and 29-32, based on Adachi in view of Virtanen, Paul, Mitchell, Nair, and Reddy. Adachi discloses mixing live bacteria with polysaccharides in a tablet. Virtanen discloses tabletting techniques related to friability. Paul discloses non-tabletted compositions comprising inulin and bacteria. Mitchell discloses non-bacteria containing tablets of inulin. Nair discloses producing non-bacteria containing tablets with inulin and other additives such as starch or calcium diphosphate. Reddy discloses bacterial tablets.

17. The invention of the '667 application, as disclosed and claimed is a method of producing tablets including live bacteria. The method comprises mixing at least one strain of live bacteria with at least one supporting substance such as fructose oligosaccharide and compressing the mixture to form a tablet having a friability of 0.1-1.0, maintaining at least about 60% viability of the bacteria following the compression. According to certain embodiments of the invention, the live bacteria may be mixed with inulin.

18. At page 4, lines 8-12 of Exhibit 1, one advantage of the invention claimed in the '667 application is summarized as follows: "The tablets according to the present invention have a lower hardness due to the lower punching pressure when the tablets are formed but an increased viability for the strain of bacteria, which makes every tablet more efficient than conventional tablets." Further, on page 5, lines 24-28, a benefit of the present invention is described thus: "the new

method results in an increased maintained viability after tablet punching of up to 200% compared with conventional tablet fillers. The increased yield results in an appreciably better economy and quality improvement of the above products."

19. I agree with the statements on page 4 of Exhibit 3 that Adachi fails to positively set forth friability of tablets, and that Adachi fails to disclose the use of fructose oligosaccharide or inulin in the method for making hard tablets with live bacteria. It is correct that Adachi does not disclose all elements of the invention of the '667 application. I do not agree with the apparent conclusion on page 3 that the Adachi disclosure of 2×10^8 bacteria after tabletting inherently discloses a tablet with at least about 60% viability of bacteria following compression.

I agree with the statements on page 4 of Exhibit 3 that Paul is silent about both hardness and friability. This is because the Paul composition is not a tablet.

20. Based on my background and experience in the field of pharmaceutical formulation it is my opinion that a person of average skill in the art of pharmaceutical formulation would recognize the disclosure and claims of the '667 application to be directed to a novel method of tablet production. Further, this person of average skill would recognize that neither Adachi, Virtanen, Paul, Mitchell, Nair nor Reddy disclose the novel method because there are significant differences in the disclosures and benefits of each respective invention.

21. In addition to the recognition that shortcomings exist when considering the references singly, there would not be any motivation or guidance apparent to a person of average skill in the art to combine the six references. Adachi and Reddy disclose tablets with bacteria but not inulin. Mitchell and Nair disclose tablets with inulin but not bacteria. Paul discloses bacteria and inulin but not in a tablet, and Virtanen discloses tablets but without inulin or bacteria.

22. Therefore, I believe a person of average skill in the art of pharmaceutical formulation would recognize the disclosure and claims of the '667 application are patentably distinct from the disclosures of Adachi, Virtanen, Paul, Mitchell, Nair and Reddy. Based on the references available at the time of the invention, it was not known that the claimed method of producing tablets including

live bacteria and supporting substance, *e.g.* inulin, where the tablet has a friability of 0.1-1.0 and maintains at least about 60% viability of the bacteria following the tablet formation was possible. But the claimed method can be performed and results in a product with unexpected benefits, including high bacterial viability. From my knowledge and experience, I know that bacterial survival in conventional tablets is approximately 20%, so the about 60% viability of the claimed method is unexpected and remarkable.

23. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

March 28, 2004
Date

Henning G. Kristensen

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 47/26, 35/66, 9/20 — A1

(11) International Publication Number: WO 97/07822

(43) International Publication Date: 6 March 1997 (06.03.97)

(21) International Application Number: PCT/SE96/01043

(22) International Filing Date: 23 August 1996 (23.08.96)

(30) Priority Data:
9502941-9 25 August 1995 (25.08.95) SE

(71) Applicant *(for all designated States except US)*: DETUM AB [SE/SE]; P.O. Box 531 82, S-400 15 Göteborg (SE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: CEDGÅRD, Lennart [SE/SE]; Skolgatan 26, S-413 02 Göteborg (SE).

(74) Agents: GRAUDUMS, Valdis et al.; Albihn West AB, P.O. Box 142, S-401 22 Göteborg (SE).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
With amended claims.
In English translation (filed in Swedish).

(54) Title: METHOD FOR THE PRODUCTION OF TABLETS BY PRESSING AND TABLETS PRODUCED BY THE METHOD

(57) Abstract

The invention relates to a method for the production of tablets by pressing of tablet material which comprises microorganisms. The method is characterized in that the tablet material also contains oligosaccharides, preferably inulin. The invention also includes tablets produced by the method according to the invention.

TITLE: Method for the production of tablets by pressing and tablets produced by the method.

TECHNICAL FIELD:

The present invention relates to a method for the production of tablets by pressing of tablet material which contains microorganisms.

PRIOR ART:

Tablets are usually produced by pressing of a pulverulent tablet mass in a suitable shape in a so-called tablet punching machine. The tablets may have different shape and be of different size and they may also be of different hardness dependent on the properties of the tablet mass and the pressure to which they are subjected during the punching of the tablets.

When the tablets are formed heat is developed as a result of the friction against the mould surfaces and the inner friction in the tablet mass. Since the tablets usually consist of chemicals and the temperature increase is not too high, this will not create any problem since the chemicals can resist this heat increase and also are cooled rapidly. However, some tablet masses contain living microorganisms, such as bacteria, which are sensitive to high temperatures and because of this some of these bacteria die during the tablet punching.

TECHNICAL PROBLEM:

Tablets which contain microorganisms, for instance in the form of bacteria, and which are intended to contain such organisms will lose a part of or all of their value when the microorganisms are destroyed during the tablet punching. This cannot be avoided by simply using a lower pressure on the conventional tablet mass and thereby creating a lower heat development since the tablet must be

subjected to a certain pressure so that it maintains its shape and is not crumbled. For known tablet masses it is not unusual that a reduction of the viability (survival) of the bacteria in the tablet is up to 80% and even more.

SOLUTION:

It has therefore always been a problem to be able to produce tablets which contain microorganisms in the form of bacteria with a lesser reduction of the viability from tablet mass to a complete tablet and therefore according to the invention a method has been obtained for the production of tablets by pressing of tablet material comprising living organisms, which is characterized in that the tablet material also contains oligosaccharides consisting of more than two monosaccharides.

According to the invention, it is suitable that the oligosaccharides consist of fructose oligosaccharides, preferably inulin.

According to the invention it is suitable that the oligosaccharides are present in an amount of 40-99.5 % by weight of the tablet material.

The tablet material according to the invention can suitably contain microorganisms consisting of lactic acid producing bacteria.

The invention also comprises tablets produced by the method according to the invention, which tablets contain oligosaccharides and microorganisms whereby the oligosaccharides suitably consist of fructose oligosaccharides, preferably inulin.

The tablets according to the invention may contain lactic acid producing bacteria as microorganisms and they may also

contain other additives such as polysaccharides, for example microcrystalline cellulose and starch, as well as other additives such as calcium diphosphate.

DETAILED DESCRIPTION:

The tablets according to the invention comprise microorganisms, preferably lactic acid producing bacteria cultures known as probiotica, which are intended to normalise or balance bacterial flora being present in the stomach and the intestine of humans or animals, but they may also contain other types of bacteria.

By mixing oligosaccharides, preferably fructose oligosaccharides, in the tablet mass as a so-called supporting substance the tablet punching is facilitated, which makes it possible to punch tablets at a lower pressure and lower heat development at the same time as the hardness of the tablet is maintained. The brittleness of the tablet, the friability, is surprisingly not changed with the tablet mass according to the present invention.

Due to this new composition, the punching pressure for the tablet making maybe reduced by up to 50% compared to conventional tablet punching methods without any reduction of the friability. This friability according to the invention will be 0.3-0.5, which is to be compared with the reference values which are accepted according to GMP (Good Manufacturing Practice) which are within the range of 0.1-1.0. The friability is expressed in percent weight reduction of the tablets when they are rotated 100 revolutions in a standard testing machine.

The amount of oligosaccharides depends on different crystalline qualities but may suitably be 99.5-40 weight percent of the total tablet mass without admixing any other supporting substance. However, if desired, known supporting

substances such as calcium diphosphate, microcrystalline cellulose and starch may be added in a suitable small amount. A smaller addition of oligosaccharides can, however, give rise to a smaller difference with regard to the viability compared with tablet masses containing only conventional supporting substances.

The tablets according to the present invention have a lower hardness due to the lower punching pressure when the tablets are formed but an increased viability for the strain of bacteria, which makes every tablet more efficient than conventional tablets. By not pressing the tablets so hard the yield of tablets for a given amount of tablet mass will also increase.

The invention will be described more in detail below by means of two examples, of which Example 1 describes a method according to the present invention and Example 2 describes a method of conventional kind.

Example 1: recipe having an active substance and tablet filling material

Str. thermophilus & L. bulgaricus	50%
Bifidobacterium animalis	0.5%
L. plantaris	0.5%
Inulin (fructose oligosaccharides)	49%
	100%

Hardness: 2.75 kp Friability: 0.3
Viability original granulate: 5E8 cfu/g
Viability tablet: 3E8 cfu/g
40% reduction of cfu (colony forming units)

Example 2: recipe having active substance and tablet filling material

Str. thermophilus & L. bulgaricus	50%
Bifidobacterium animalis	0.5%
L. plantaris	0.5%
Calcium diphosphate	20%
Microcrystalline cellulose	18%
Starch	11%
	100%

Hardness: 5.5 kp Friability: 0.3%
Viability original granulate: 5E8 cfu/g
Viability tablet: 1E8 cfu/g
80% reduction of cfu (colony forming units)

As appears from the above examples, the friability is maintained unchanged with a value of 0.3 whereas the hardness has been decreased to 2.75 kp compared with 5.5 kp for the conventional method. The viability has increased from 1E8 cfu/g to 3E8 cfu/g according to the invention. The reduction of cfu from tablet mass to tablet during the tablet punching became only 40% according to the new method and 80% according to the conventional method.

Accordingly, the new method results in an increased maintained viability after tablet punching of up to 200% compared with conventional tablet fillers. The increased yield results in an appreciably better economy and quality improvement of the above products.

The invention is not limited to the embodiments shown above but can be varied in different ways within the scope of the claims.

CLAIMS:

1. Method for the production of tablets having high viability in the tablet by pressing tablet material containing living microorganisms, c h a r a c t e r i z e d i n that the tablet material also contains oligosaccharides.

2. Method according to claim 1 c h a r a c t e r i z e d i n that the oligosaccharides are present in an amount of 40-99.5 percent by weight of the tablet material.

3. Method according to any of claims 1-2, c h a r a c t e r i z e d i n that the oligosaccharides consist of fructose oligosaccharides.

4. Method according to any of claims 1-3, c h a r a c t e r i z e d i n that the oligosaccharides consist of inulin.

5. Method according to any of claims 1-4, c h a r a c t e r i z e d i n that the microorganisms consist of lactic acid producing bacteria.

6. Tablets produced according to any of claims 1-5 containing oligosaccharides and microorganisms.

7. Tablets according to claim 6, c h a r a c t e r i z e d i n that the oligosaccharides consist of fructose oligosaccharides.

8. Tablets according to any of claims 6-7, c h a r a c t e r i z e d i n that the oligosaccharides consist of inulin.

9. Tablets according to any of claims 6-8, c h a r a c t e r i z e d i n that the microorganisms consist of lactic acid producing bacteria.

10. Tablets according to any of claims 6-9, c h a r a c t e r i z e d i n that they also contain polysaccharides such as microcrystalline cellulose and starch as well as other additives such as calcium diphosphate.

AMENDED CLAIMS

[received by the International Bureau on 24 December 1996 (24.12.96); original claims 1 - 10 replaced by amended claims 1 - 10 (2 pages)]

1. Method for the production of tablets having high viability in the tablet by pressing tablet material containing living microorganisms, c h a r a c t e r i z e d i n that the tablet material also contains oligosaccharides consisting of more than two monosaccharides.

2. Method according to claim 1 c h a r a c t e r i z e d i n that the oligosaccharides are present in an amount of 40-99.5 percent by weight of the tablet material.

3. Method according to any of claims 1-2, c h a r a c t e r i z e d i n that the oligosaccharides consist of fructose oligosaccharides.

4. Method according to any of claims 1-3, c h a r a c t e r i z e d i n that the oligosaccharides consist of inulin.

5. Method according to any of claims 1-4, c h a r a c t e r i z e d i n that the microorganisms consist of lactic acid producing bacteria.

6. Tablets produced according to any of claims 1-5 containing oligosaccharides and microorganisms.

7. Tablets according to claim 6, c h a r a c t e r i z e d i n that the oligosaccharides consist of fructose oligosaccharides.

8. Tablets according to any of claims 6-7, c h a r a c t e r i z e d i n that the oligosaccharides consist of inulin.

9. Tablets according to any of claims 6-8, characterized in that the microorganisms consist of lactic acid producing bacteria.

10. Tablets according to any of claims 6-9, characterized in that they also contain polysaccharides such as microcrystalline cellulose and starch as well as other additives such as calcium diphosphate.

CLAIMS:

Claims 1 - 10 (cancelled)

11. (Previously amended) A method of producing a tablet including live bacteria comprising the steps:
    a) mixing at least one strain of said live bacteria with at least one fructose oligosaccharide to form a mixture,
    b) compressing said mixture so as to form said tablet having a friability of between 0.1 and 1.0 while maintaining at least about 60% viability of said bacteria following the compression.

12. (Previously amended) The method of claim 11 wherein said fructose oligosaccharide is present in an amount of about 40 – 99.5% by weight of said tablet.

13. (cancelled)

14. (Previously amended)The method of claim 11 wherein said fructose oligosaccharide is inulin.

15. (Previously added)The method of claim 11 wherein said bacteria are lactic acid producing bacteria.

16. (Previously amended) A method of producing a tablet including live bacteria comprising the steps:
    a) mixing at least one strain of live lactic acid producing bacteria with at least one fructose oligosaccharide to form a mixture; and
    b) compressing said mixture so as to form said tablet having a friability of between 0.1 – 1.0 while maintaining at least about 60% viability of said lactic acid-producing bacteria.

17. (Previously amended) The method of claim 16 wherein said fructose oligosaccharide is inulin.

18. (Previously amended) The method of claim 16 further comprising adding at least one pharmaceutically acceptable additive to said bacteria and said fructose oligosaccharide prior to said pressing step.

19. (Previously amended) The method of claim 16 further comprising adding microcrystalline cellulose to said bacteria and said fructose oligosaccharides prior to said pressing step.

20. (Previously amended) The method of claim 16 further comprising adding starch to said bacteria and said fructose oligosaccharide prior to said pressing step.

21. (Previously amended) The method of claim 16 further comprising adding calcium diphosphate to said bacteria and said fructose oligosaccharide prior to said pressing step.

22. (Previously amended) A method of producing a tablet including live bacteria comprising the steps:
    a) mixing live bacteria *Str. Thermophilus, L. Bulgaricus, Bifidobacterium animalmis,* or *L. Plantaris* with inulin to produce a mixture; and
    b) compressing said mixture so as to form said tablet having a friability of between 0.1 – 1.0 while maintaining at least about 60% viability of said bacteria.

23. (Previously added)The method of claim 22 further comprising adding at least one pharmaceutically acceptable additive to said live bacteria and said inulin.

24. (Previously added) The method of claim 22 further comprising adding calcium diphosphate to said live bacteria and said inulin.

25. (Previously added) The method of claim 22 further comprising adding microcrystalline cellulose to said live bacteria and said inulin.

26. (Previously added) The method of claim 22 further comprising adding starch to said live bacteria and said inulin.

27. (Previously amended) A method of producing a tablet including live bacteria comprising the steps;

a) mixing at least one live bacteria selected from the group consisting of *Str. Thermophilus, L. Bulgaricus, Bifidobacterium animalmis* and *L. Plantaris* with inulin and at least one additive selected from the group consisting of microcrystalline cellulose, calcium diphosphate and starch; and

b) compressing said mixture so as to form said tablet having a friability of between 0.1 – 1.0 and maintain at least about 60% viability of said *Str. Thermophilus, L. Bulgaricus, Bifidobacterium animalmis* and *L. Plantaris* bacterium.

28. (Cancelled)

29. (Previously added) The method of claim 11, wherein the friability of the tablet is between 0.3 and 0.5.

30. (Previously added) The method of claim 16, wherein the friability of the tablet is between 0.3 and 0.5.

31. (Previously added) The method of claim 22, wherein the friability of the tablet is between 0.3 and 0.5.

32. (Previously added) The method of claim 27, wherein the friability of the tablet is between 0.3 and 0.5.

AMN

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/465,667	12/17/1999	LENNART CEDGARD	ALBIHN-W-3.3 -258CON	9154

530 7590 01/13/2004

LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK
600 SOUTH AVENUE WEST
WESTFIELD, NJ 07090

Due
13APR2004

EXAMINER	
AFREMOVA, VERA	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	09/465,667	CEDGARD, LENNART
	Examiner	Art Unit
	Vera Afremova	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *11,12,14-27 and 29-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *11,12,14-27 and 29-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/20/2003 has been entered.

Status of claims

Claims 11, 12, 14-27 and 29-32 as amended 10/20/2003 are pending and under examination. Claims 1-10 were canceled by applicant in Preliminary amendment [paper No. 8 filed 2/05/2001]. Claim 13 was canceled by applicant [Paper No. 11 filed 5/21/2001]. Claim 28 was canceled by applicant [Paper No. 20 filed 8/07/2002].

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). However, it is uncertain whether the certified copy has been filed in parent Application No. 09/029,336. Please, provide evidence of filing or certified copy the foreign priority documents.

Specification

The disclosure is objected to because of the following informalities:

Please, insert in the first sentence of the specification updated information about continuing data and domestic priority based on 09/029,336. Appropriate correction is required.

Response to Arguments

Applicant's arguments filed 10/20/2003 with regard to claims rejection under 35 U.S.C. 112 have been fully considered and found persuasive as related to the pending claims as presently amended. Thus, claim rejections under 35 U.S.C. 112, *first and second paragraphs*, have been withdrawn.

Claim Rejections - 35 U.S.C. § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 11, 12, 14-27 and 29-32 as amended are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,396,631 taken with US 5,536,526; US 5,531,989; US 5,422,346; US 4,021, 545 and US 4,806,368

The claims are directed to a method for producing tablets with live bacteria comprising step of mixing live bacteria with fructose oligosaccharide or inulin and step of compressing the mixture into tablets. The final compressed tablet is characterized by good friability within 0.1-1.0 and by bacterial viability after compressing tablets of about 60%. Some claims are/are further drawn to the use of particular species of bacteria such as *Lactobacillus bulgaricus, Lactobacillus plantarum, Streptococcus thermophilus or Bifidobacterium animalis* in the method for producing tablets with live bacteria. Some claims are further drawn to the use of fructose oligosaccharide or inulin at concentration 40-99.5% in the tablet in the method for producing tablets with live bacteria. Some claims are further drawn to incorporation of additives into the tablet including starch or calcium diphosphate in the method for producing tablets with live bacteria.

US 4,396,631 teaches a method for producing hard tablets with live bacteria wherein the method comprises step of mixing live bacteria with binding materials and additives including starch, sugar, gelatin and others additives suitable for forming tablets and step of compressing the mixture in order to form tablets with viable bacteria. The cited patent clearly discloses that bacteria retain high viability ($2x10^8$ cfu) after formation of the compressed tablets as well as during storage of the compressed tablets (col. 4, example 1).

The cited patent US 4,396,631 is silent with regard to friability of tablets. However, it is well established in the art that compressed tablets have friability of about 0.3 according to good manufacturing practice as demonstrated by US 5,536,526 (col. 4, lines 7-10).

The cited patent US 4,396,631 is lacking the disclosure about the use of fructose oligosaccharide or inulin in the method for making hard tablets with live bacteria.

However, US 5,422,346 teaches the use of fructose oligosaccharide or inulin in the method for producing hard tablets and it also teaches that inulin is compressed into tablets without the need of additional binding materials such as starch, for example: col. 8, lines 41-44. The cited patent US 5,422,346 also teaches that inulin is a suitable substrate for promoting growth of beneficial bacteria such as lactic bacteria including *Bifidobacterium sp* and that the pathogenic enteric bacteria cannot utilize inulin, unlike the beneficial bacteria in the gastrointestinal tract of animals (col. 18, lines 25-37).

US 5,531,989 is relied upon to demonstrate a method for producing dry agglomerates with live lactic bacteria by using fructose oligosaccharide or inulin wherein the final products comprise about 40-60 % by weight of inulin and/or fructose oligosaccharide and about 0.1-20% by weight of live lactic bacteria of *Lactobacillus sp.* and /or *Bifidobacterium sp.* including *L. bulgaricus* and *L. plantarum* (col. 13, lines 38-50 and col. 4, lines 1-30). Although the cited patent US 5,531,989 is silent about hardness and/or friability of the final agglomerated products, it clearly teaches the use of live lactic bacteria in combination with inulin in the method of producing agglomerates wherein the final agglomerated products contain viable bacteria.

In addition, US 4,021, 545 is relied upon for the disclosure about the use of various materials including inulin, starch, calcium diphosphate and others in the methods for producing hard tablets (col. 5, example 4).

And US 4,806,368 is relied upon for the disclosure about the use of various materials including vitamins, cellulose or fibers in the methods for producing hard tablets (col. 5, example 4). The cited US 4,806,368 also teaches that hard tablets allow for prolonged storage of live bacteria containing tablets when compared to the dry agglomerated powders.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to substitute inulin for starch or to add inulin into the tablets in the method for making hard tablets with viable bacteria in the method of US 4,396,631 with a reasonable expectation in success for producing hard tablets with viable bacteria because inulin has been taught as a substitution for the other binding agents including starch in the hard tablets {US 5,422,346; US 4,021,545} and because inulin has been demonstrated in the products with live bacteria {US 5,531,989} as adequately demonstrated by the cited prior art. One ordinary of skill in the art would have been motivated to incorporate inulin in the live bacteria-containing tablets for the expected gastrointestinal health benefits upon administration of these tablets because inulin is a beneficial substrate for promoting growth of beneficial probiotic bacteria including lactic bacteria and because inulin is not readily utilized by pathogenic enteric bacteria {US 5,422,346}. Thus, incorporation of inulin in the live-bacteria-containing tablets provides for the effects of the competitive exclusion of pathogenic bacteria by beneficial probiotic bacterial preparations {US 5,422,346; US 5,531,989}. One ordinary of skill in the art would also have been motivated to make hard tablets with live lactic bacteria because the hard tablets allow for

preservation of the viability of live lactic bacteria for longer periods of storage unlike the dry bacterial powders as adequately taught by the prior art {US 4,806,368}. Accordingly, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351 till January 15, 2004 or (571) 271-0914 after January 15, 2004. The examiner can normally be reached on 9.30 am - 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (703) 308-4743 till January 15, 2004 or on (571) 272-0926 after January 15, 2004.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Vera Afremova

AU 1651

January 7, 2004.

V. Afremova

VERA AFREMOVA

PATENT EXAMINER